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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/977,864

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Henryk Dudek

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ROPES & GRAY LLP  
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EXAMINER

HOWARD, ZACHARY C

ART UNIT

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12/04/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 09/977,864	<b>Applicant(s)</b> DUDEK ET AL.	
	<b>Examiner</b> ZACHARY C. HOWARD	<b>Art Unit</b> 1646	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 18 August 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,5,6,8,21 and 23-70 is/are pending in the application.
- 4a) Of the above claim(s) 6 and 8 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,5,21 and 23-70 is/are rejected.
- 7) ☒ Claim(s) 67 is/are objected to.
- 8) ☒ Claim(s) 1,5,6,8,21 and 23-70 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 14 April 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>8/18/09</u> .   | 6) <input type="checkbox"/> Other: _____                          |

## DETAILED ACTION

### ***Status of Application, Amendments and/or Claims***

The amendment of 8/18/09 has been entered in full. Claims 4 and 9 are canceled.

Claims 1, 5, 6, 8, 21 and 23-70 are pending.

Claims 6 and 8 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims are 1, 5, 21 and 23-70 are under consideration.

### ***Withdrawn Objections and/or Rejections***

The following page numbers refer to the previous Office Action (6/19/09).

The objection to the specification at pg 4 is *withdrawn* in view of Applicants' amendments to the title of the specification.

The provisional rejection at pg 2-3 of claims 1, 5, 21, 25, 26, 28, 30, 31, 35, 36, 38-43, 50-53 and 56-59 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 52, 56-59, 68, 72, 76-79, 90-93, 95 and 97 of copending Application No. 10/652,298 is *withdrawn* in view of the terminal disclaimer naming Application No. 10/652,298 filed by Applicants on 8/18/09 and approved by the USPTO on 9/20/09.

The provisional rejection at pg 3-4 of claims 61 and 64-67 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 23, 25-27, 29-31, 33, 34, 35, 37, 38, 53-55, 60-64, 69-71, 73-75, 80, 81, 84-87, 90-93, 96, 98 and 100 of copending Application No. 10/652,298 is *withdrawn* in view of the terminal disclaimer naming Application No. 10/652,298 filed by Applicants on 8/18/09 and approved by the USPTO on 9/20/09.

The rejection at pg 4-7 of claims 21, 25, 35, 50, 51, 61, 64, 65 and 67 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13, 19, 21, 23, 25, 27-30, 32, 34-37, 39-44, 45-50, 53-56, 59-62, 64 and 66 of

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U.S. Patent No. 7,498,304 is *withdrawn* in view of the terminal disclaimer naming Patent No. 7,498,304 filed by Applicants on 8/18/09 and approved by the USPTO on 9/20/09.

Please see new claim objections and rejections below.

### ***New Claim Objections and/or Rejections***

#### ***Claim Objections***

Claim 67 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants are required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 67 limits the method of parent claim 64 to one "wherein the tumor overexpresses a *Sonic hedgehog* gene". However, parent claim 64 is already limited to a *Sonic hedgehog* gene. When claim 67 was originally presented in the amendments filed 6/11/08, parent claim 64 recited *gli-1* and *Sonic hedgehog* in the alternative. However, in a subsequent amendment, the limitation directed to *gli-1* was deleted from claim 64. Therefore, claim 67 does not currently further limit parent claim 64.

#### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 61-70 are rejected under 35 U.S.C. 102(e) as being anticipated by Ling et al, US Patent Application Publication 2003/0022819 (published 1/30/2003 and claiming priority to 6/16/2000; reference AA1 on the 12/13/2007 IDS). The earliest date to which the instant application claims priority is 10/13/00.

Claims 61-70 each encompass a method for treating a tumor associated with colon cancer comprising determining or ascertaining whether the tumor overexpresses

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a *Sonic hedgehog* gene, and administering a hedgehog antibody that binds to Sonic hedgehog (Shh) protein and inhibits hedgehog signaling, whereby the growth or proliferation of the tumor is decreased. The recitations of "determining" or "ascertaining" whether the "tumor" or "colon cancer tissue" "overexpresses a *Sonic hedgehog* gene" encompasses determining overexpression by measuring the expression of Shh protein.

Ling et al teach that they "determined that hedgehog protein is overexpressed in several human gastrointestinal tumor cell lines compared to normal human gastrointestinal epithelial cells or fibroblasts (Example 7) and that inhibition of hedgehog using, for example, anti-hedgehog blocking antibody, may decrease tumor growth rate and/or tumor angiogenesis (Example 7)" (§ 552). Example 7 is titled "Inhibition of Hedgehog (Anti-Hedgehog blocking antibody) Decreases Tumor Growth Rate and/or Tumor Angiogenesis)" (pg 44, § 635). Example 7 teaches a method of determining that hedgehog protein is overexpressed in "several human gastrointestinal tumor cell lines compared to normal human gastrointestinal epithelial cells or fibroblasts" (§ 639). The gastrointestinal epithelial cell lines used are each colon cancer cell lines, including T84 (CCL-284), Caco2 (HTB-37) and SW480 (CCL-228) (§ 636). Example 7 further teaches use of "hedgehog-blocking or hedgehog pathway-blocking reagents such as the anti-hedgehog blocking antibodies (5E1, AP.G6, AI.C9 or BH.E4) to inhibit tumor angiogenesis and tumor growth .... in subcutaneously-implanted tumor models"; "[c]arcinoma cell lines of gastrointestinal origin such as SW480, HT29 or T84 are passaged in nude mice as subcutaneous tumors or are passaged in culture"; "cells ... fragments of passaged tumors are implanted subcutaneously"; and "[m]ean tumor weight change and/or mean vascular density are decreased in the hedgehog blocking antibody-treated group compared to the antibody-treated group" (§ 640).

Thus, Ling et al teach a method of determining or ascertaining whether a tumor (e.g., the orthotopic tumor) overexpresses a *Sonic hedgehog* gene (e.g., by measuring Shh protein expression in the tumor cell line used to create the tumor), and administering a hedgehog antibody that binds to Sonic hedgehog protein and inhibits hedgehog signaling, whereby the growth or proliferation of the tumor is decreased. Therefore, the teachings of Ling et al anticipate claims 61-70.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicants are advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 21 and 23-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ling et al, US Patent Application Publication 2003/0022819 (published 1/30/2003 and claiming priority to 6/16/2000; reference AA1 on the 12/13/2007 IDS). The earliest date to which the instant application claims priority is 10/13/2000.

Claims 1, 5, 21 and 23-60 each encompass a method for treating a tumor associated with colon cancer comprising determining or ascertaining whether the tumor overexpresses a *gli-1* gene, wherein said overexpression indicates administration of a hedgehog antagonist is appropriate, and administering a hedgehog antibody that binds to Sonic hedgehog (Shh) protein and inhibits hedgehog signaling, whereby the growth or proliferation of the tumor is decreased, and wherein determining *gli-1* gene overexpression comprises determining *gli-1* protein or transcript expression.

The teachings of Ling et al are described above. Ling et al does not teach determining or ascertaining that the tumor associated with colon cancer overexpresses

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the gli-1 gene by determining gli-1 protein or transcript expression, or wherein said overexpression indicates that administering the hedgehog antibody is appropriate.

Ling et al further teach a cell line that is "hedgehog responsive" and that "[h]edgehog treatment of the cells causes an upregulation of gli-1 and patched-1 (known indicators of hedgehog dependent signaling)" (§ 139). Ling et al further teach that "Shh treatment also produces a dose-dependent increase in gli-1 and ptc-1 expression, which can readily be detected by PCR-based analysis" (§ 540). Detection of gli-1 expression by PCR-based analysis is equivalent to detection of gli-1 transcript.

It would have been obvious to the skilled artisan at the time the invention was made to substitute determination of gli-1 gene overexpression by measuring gli-1 protein for the determination of Shh gene overexpression by measuring Shh protein in the method taught by Ling et al. The skilled artisan would have been motivated to make such changes to provide alternate markers (i.e., a second confirming marker) for detection of a tumor that overexpresses the hedgehog signaling pathway and is thus responsive to anti-hedgehog antibody treatment. Furthermore, use of gli-1 gene transcript (rather than just the protein as for Shh) would have further been motivated by the teaching that gli-1 expression can be readily be detected by PCR-based analysis. The skilled artisan would have had a reasonable expectation of success in making and using each substitution because Ling et al teaches that certain tumor cells overexpress the Sonic hedgehog protein, that Shh treatment increases gli-1 expression, that gli-1 is a known indicator of hedgehog dependent signaling, and thus each substitution would be a simple substitution of one known element for another known element.

### ***Conclusion***

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./  
Examiner, Art Unit 1646

/Bridget E Bunner/  
Primary Examiner, Art Unit 1647